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(54) Title: TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

(57) Abstract

Tomoxetine, a norepinephrine uptake inhibitor, is used to treat attention-deficit/hyperactivity disorder.

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TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The invention belongs to the fields of pharmaceutical chemistry and psychiatric medicine, and provides a method of treatment of the psychiatric disorder known as attention-deficit/hyperactivity disorder.

Background of the Invention

For some decades it has been recognized that a significant number of children are persistently hyperactive and have an attention span so short as to be disabling in school and in many personal relationships. Such children in earlier times would no doubt have been dismissed as incorrigible and punished or even confined in an institution. Some long time ago, however, it was realized that these children cannot control their hyperactivity and inattention, and the medical professions began to try to help them. Methylphenidate (Ritalin™)has been used for some time to treat such children and it often significantly improves their ability to function and coexist with other people at school and at home. However, the drug has the disadvantages of requiring several doses per day, and producing a rebound effect as the effect of each dose fades away. Further, the drug causes sleeplessness and lack of appetite in some patients. Methylphenidate has both noradrenergic and dopaminergic activities.

Imipramine, desipramine, nortriptyline, amitriptyline and clomipramine are also used in some cases of attention-deficit/hyperactivity disorder (ADHD). Those tricyclic drugs, however, have a number of physiological mechanisms and, as a class, tend to produce a number of side effects and require careful supervision and dose titration.

In the last decade, psychiatrists have realized that ADHD is not only a disorder of childhood, but often continues in the adult. It is obvious that hyperactivity and short attention span cause grave disruption in an adult's

life, but it is only recently that such patients have been able to obtain any treatment.

The need for a safe and convenient treatment for ADHD, applicable to both children and adults and without the disadvantages possessed by methylphenidate continues to be a concern of the psychiatric profession.

The present invention provides a method of treating attention-deficit/hyperactivity disorder comprising the administration to a patient in need of such treatment of an effective amount of tomoxetine.

The invention also provides the use of tomoxetine for the manufacture of a medicament for treating attention-deficit/hyperactivity disorder; and the use of tomoxetine for treating attention-deficit/hyperactivity disorder.

Tomoxetine is a well-known drug, the chemical name of which is (R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine. It is regularly used as a salt, and salts are included in the term tomoxetine as used here. See, for example, Gehlert, et al., Neuroscience Letters 157, 203-06 (1993), for a discussion of the mechanism of tomoxetine's activity as a norepinephrine reuptake inhibitor. Tomoxetine is quite active in that function, and moreover is substantially free of other central nervous system activities at the concentrations or doses at which it effectively inhibits norepinephrine reuptake. Thus, it is quite free of side effects and is properly considered to be a selective drug.

Tomoxetine is a notably safe drug, and its use in ADHD, in both adults and children, is a superior treatment for that disorder because of its improved safety. Further, tomoxetine is effective at relatively low doses, as discussed below, and may safely and effectively be administered once per day. Thus, difficulties created by the multiple dosing of patients, particularly children and disorganized adults, are completely avoided.

The effective dose of tomoxetine for ADHD is in the range from about 5 mg/day to about 100 mg/day. The preferred adult dose is in the range from about 10 to about 80 mg/day, and a more highly preferred adult dose is from about 20 to about 60 mg/day. The children's dose of course is smaller, in the range from about 5 to about 70 mg/day, more preferably from about 10 to about 60 mg/day and still more preferably from about 10 to about 50 mg/day. The optimum dose for each patient, as always, must be set by the physician in charge of the case, taking into account the patient's size, other medications which the patient requires, severity of the disorder and all of the other circumstances of the patient.

Since tomoxetine is readily orally absorbed and requires only once/day administration, there is little or no reason to administer it in any other way than orally. It may be produced in the form of a clean, stable crystal, and thus is easily formulated in the usual oral pharmaceutical forms, such as tablets, capsules, suspensions, and the like. The usual methods of pharmaceutical scientists are applicable. It may usefully be administered, if there is any reason to do so in a particular circumstance, in other pharmaceutical forms, such as injectable solutions, depot injections, suppositories and the like, which are well known to and understood by pharmaceutical scientists. It will substantially always be preferred, however, to administer tomoxetine as a tablet or capsule and such pharmaceutical forms are recommended.

The ADHD patient is rather readily recognized, and most people have been in contact with children, if not adults, who exhibit some or all of the symptoms of the disorder. The best description of the disorder is the diagnostic criteria for ADHD, published by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Version (1994), as follows.

Diagnostic criteria for Attention-Deficit/ Hyperactivity Disorder

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)

(h) is often easily distracted by extraneous stimuli

(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often "on the go" or often acts as if "driven by a motor"

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

It will be seen that ADHD is a disorder made up of two components, the attention deficit component and the hyperactivity component, which are to a degree independent. Treatment with tomoxetine is effective in patients who are primarily suffering from either component or from the combined disorder.

While ADHD is still primarily regarded as a disorder of children, it is now understood that many ADHD patients, as many as 50%, continue to suffer from the disorder as they grow through adolescence into adulthood. Biederman and associates have extensively studied the adult ADHD patient, and have found numerous cases. See, for example, Biederman, et al., Am. J. Psychiatry 150, 1792-98 (1993). They found that cases of adult ADHD were frequently found among the parents and adult siblings of childhood ADHD patients. Thus, it appears that the disease is not only carried forward into adulthood, but is inheritable.

The Biederman, et al. article cited immediately above, as well as another article by the same authors, Am. J. Psychiatry 148, 564-77 (1991), reports studies of ADHD patients who also have one or more other psychiatric disorders. The authors indicate that such psychiatric co-morbidity is quite common among ADHD patients and, naturally, cloud the diagnosis and treatment of such patients. Tomoxetine is effective in the treatment of ADHD, even though

the situation of the treated patient may be complicated by co-morbidity with one or more additional disorders.

The mere listing of the above diagnostic criteria indicates the seriousness of ADHD and the damage which it does to the patient. A person having a moderately severe case of ADHD is substantially entirely unable to concentrate and hence unable to do meaningful work or study; is a continuing distraction and nuisance to those around her or him, because of the uselessly impulsive activity which the disorder causes; and consumes his or her family in cleaning up and repairing the damage and disruption which he or she causes. Such a patient of school age may substantially damage the teacher's ability to accomplish the class' goals, because the ADHD child will continually disrupt the class, distract the other children and consume the teacher's effort. Thus, it is readily apparent that an improved treatment of ADHD is needed, and that the present invention is accordingly important to many people.

The method of the present invention is effective in the treatment of patients who are children, adolescents or adults, and there is no significant difference in the symptoms or the details of the manner of treatment among patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to be a patient below the age of puberty, an adolescent is considered to be a patient from the age of puberty up to about 18 years of age, and an adult is considered to be a patient of 18 years or older.

Claims

1. A method of treating attention-deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of tomoxetine.

2. A method of Claim 1 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

3. A method of Claim 1 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

4. A method of Claim 1 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

5. A method of Claim 1 wherein the patient is an adult.

6. A method of Claim 5 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

7. A method of Claim 5 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

8. A method of Claim 5 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

9. A method of Claim 1 wherein the patient is an adolescent.

10. A method of Claim 9 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

11. A method of Claim 9 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

12. A method of Claim 9 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

13. A method of Claim 1 wherein the patient is a child.

14. A method of Claim 13 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

15. A method of Claim 13 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

16. A method of Claim 13 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

INTERNATIONAL SEARCH REPORT

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PCT/US96/00091

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/16, 9/20, 9/48
US CL :424/464, 451, 489

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 451, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RYAN, NEAL D. Heterocyclic Antidepressants in Children and Adolescents. Journal of Child and Adolescent Psychopharmacology. 1990, Vol. 1, No. 1, pages 21, 22, and 30.	1-16
Y	GREEN, WAYNE H. Nonstimulant Drugs in the Treatment of Attention Deficit Hyperactivity Disorder. Child and Adolescent Psychiatric Clinics of North America. October 1992, Vol. 1, No.2, pages 451 and 457.	1-16
Y	WONG et al. A New Inhibitor of Norepinephrine Uptake Devoid of Affinity for Receptors in Rat Brain. The Journal of Pharmacology and Experimental Therapeutics. 26 March 1982, Vol. 222, No.1, pages 61 and 64.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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